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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 19

Application Number: 10/010,283
Filing Date: November 13, 2001
Appellant(s): BAUER ET AL.

Janis K. Fraser, Ph.D, J.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 29, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant states that the claims should stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

WO 93/11773	Carling et al.	06-1993

(U) Cazzola et al. "Effect of Salmeterol and formoterol in Patients with Chronic Obstructive Pulmonary Disease" Pulmonary Pharmacology vol. 7, no. 2 (1994), pages 103-107.

(V)Nederlands Tijdschrift voor Geneeskunde, "Opportunistic lung infection in patients with chronic obstructive pulmonary disease; a side effect of inhalation corticosteroids". 1996m 140/2, pages 94-98.

(W) Saunders Manual of Medical Practice (1996).

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 9, 11-25 are rejected under 35 U.S.C. 103(a) in view of Carling et al. (WO 93/11773), in view of Cazzola et al.(U), and Nederland Tijdschrift Voor Geneeskunde (V), in view of Saunders Manual of Medical Practice (W). This rejection is set forth in prior Office Action, Paper No. 13.

(11) Response to Argument

Applicants' argument that in light of the prior art at the time the invention was made, including the references cited by the Examiner, there would not have been a reasonable expectation of success regarding the treatment of COPD with a combination of budesonide and formoterol because Carling et al. does not teach or suggest that his combination of formoterol and budesonide is suitable for treating COPD and that Carling et al. mentions that his combination of formoterol and budesonide is suitable for treating "respiratory diseases," and the only specific

respiratory disease mentioned is asthma which is separate and distinct from COPD. This argument has been considered but is not persuasive for reasons discussed below.

Applicants assert that Carling et al. mentions that his combination of formoterol and budesonide is suitable for treating "respiratory diseases", addition to this assertion, it is noted that Carling et al. also teach that this combination is useful and effective for the respiratory disorders other than asthma. (page 2, lines 3-4). On page 2, lines 3-4, Carling et al. stated that "This invention relates to improvements in the treatment of mild as well as severe asthma and **other respiratory disorder**." Carling et al. on page 1, lines 12-13, clearly teaches the treatment of respiratory disorders **such as** asthma and **other respiratory disorders**. The term "**such as**" is merely an example of one of respiratory disorders and does not exclude **other** respiratory disorders generally taught by Carling et al. Applicants' claiming COPD is well-known by Saunder's Manual of Medical Practice (W) as on of Respiratory disorder and this reference is cited by the Examiner. Applicants assert that asthma and COPD are separate and distinct diseases. However, again, they are well-known respiratory disorders as taught by Saunder's Manual of Medical Practice (W) and the combination comprising Applicants active agents are taught by Carling et al. to be effective not only for the asthma but **other respiratory disorders** such as COPD. Therefore, a reasonable expectation of success that Carling et al's combination would work in asthma as well as other respiratory disorders, e.g. COPD as disclosed by the (W) reference as long as one were willing to treat other respiratory disorder, e.g. COPD. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Carling et al. teach the combination is useful for the treatment of respiratory disorder and that COPD is one of respiratory disorder as listed by (W) reference. Therefore, it would have been obvious to one of ordinary skill in the art to utilize Carling et al.'s combination for the treatment of any respiratory disorders such as COPD with reasonable expectation of success. It is noted that one of active agent, formoterol, is alone can incrase FEV in COPD patients by up to 15% as taught by (U) reference. Therefore there is a reasonable expectation of successfully treating COPD utilizing Carling et al's combination comprising formoterol as one of active agent for the treatment of COPD (respiratory disorder).

Applicants cited (Jeffrey PK, Thorax 53:129-36, 1998) and argue that Airway inflammation in COPD, for example, differs from airway inflammation in asthma. However, this reference is irrelevant since Carling et al. teach that Applicants' combination is useful for the respiratory disorders such as asthma **and other respiratory disorders**. Therefore, one would have been motivated to employ the combination to treat other respiratory disorders (e.g. COPD) with reasonable expectation of successfully treating other well-known respiratory disorders listed by the (W) reference.

Applicants' rebuttal argument, asserting (V) reference is much less clear for the place of corticosteroid in the treatment of patients with COPD because patients suffering from COPD were treated with budesonide and subsequently, half (n=2) of the patients developed infections and that the authors concluded that long term inhalation corticosteroid treatment should be

prescribed in COPD patients only if the efficacy of the medication has been proved in the individual patient. This is not persuasive because (V) reference teaches the treatment of COPD employing relatively high dose of budesonide per day and the high dosages of inhalation corticosteroids may have been involved in the cause of these infections. Moreover, the authors' conclusion is drawn to only a long-term use of corticosteroid should be prescribed in COPD patients with efficacy of the medication has been proved in the individual patient involved. The Examiner's position is that this teaching does not exclude short-term treatment of corticosteroid inhalation for the treatment of COPD and the low dose of corticosteroid. Therefore, it would be obvious to one of ordinary skill in the art to employ Carling et al's composition for the short-term treatment of COPD since a long-term use with relatively high dose of corticosteroid may have involved in the infection.

Applicants' rebuttal argument that (U) reference teaches the treatment with formoterol alone can increase FEV in COPD patients by up to 15%, in light of the teachings of reference (V), it certainly would not have been obvious to combine budesonide with formoterol, or any other drug, for the treatment of COPD because one of ordinary skill in the art might have concluded that the prescription of budesonide to treat COPD would be a treatment-of-last resort, given the increased risk of opportunistic pulmonary infections. This is not persuasive because the combination is well-taught by Carling et al. for the treatment of respiratory disorders. Further, the effectiveness of formoterol (one of active agent) alone is taught by the prior art (U) reference for the treatment of COPD and the fact that the (V) reference used budesonide for the patients suffered from COPD. The (V) reference is clear that infection was caused by relatively high dose of corticosteroid and further suggesting that it can still be used in long-term inhalation

treatment in COPD patients if the efficacy of the medication has been proved in the individual patients. It is noted that Applicants' claims are drawn to effective amount of treatment of COPD regardless of the duration of the treatment (i.e. acute or chronic (long-term)) and that prior art does not exclude acute or short term treatment using budesonide. Therefore it would have been obvious to one of ordinary skill in the art to utilize the combination effective for the treatment of respiratory disorders as taught by Carling for the treatment of COPD because formoterol alone is effective for the treatment of COPD and budesonide is also used in COPD patients. One of ordinary skill in the art would have been motivated to utilize the combination taught by Carling et al. for the treatment of COPD because one of the active agent (formoterol) is effective for the treatment of COPD as taught by (U) reference and budesonide can be used for the short term treatment with relatively low dosages for the treatment of COPD in order to achieve expected benefit of treating COPD (respiratory disorder) and to avoid the infection caused by relatively high does of budesonide as taught by the prior art.

Applicants' rebuttal argument that the Declaration of Jan Trofast ("the Trofast declaration"), submitted with Applicants' reply filed April 25, 2002, supports Applicants' position that Carling's teaching of the use of budesonide and formoterol to treat asthma would not have suggested their use to treat COPD because at the time the application was filed, the difficulties of treating COPD and the general lack of enthusiasm for the treatment methods (including the use of glucocorticoids, such as budesonide and steroids) and assert that Pauwels et al. and Niewoehner having limited beneficial effects in treatment of COPD than asthma. This is not persuasive because these references shows that budesonide has some benefit in treatment of COPD, it may be less effective compare to treatment of asthma, it still indicates the

effectiveness of budesonide in treatment of COPD. In the Trofast Declaration number 7, line 5, reports that benefits were found in using budesonide for the treatment of COPD in short term; the declaration number 8, state that benefits of systemic glucocorticoids in treating acute exacerbation of COPD were much smaller than the benefit of glucocorticoids in treatment of severe asthma. This report therefore is indication that there is some benefit of budesonide in treatment of COPD. Now, this benefit may be much smaller than for the treatment of asthma, but there is some benefit of treating COPD with budesonide.

Applicants' rebuttal argument that in declaration, Dr. Trofast presented data indicating that treatment of COPD with both budesonide and formoterol was more effective than treatment with either drug alone and the declaration of Christer Hultquist demonstrating a synergistic effect of the combination treatment on the severe exacerbations phenotype have been considered, but is found unpersuasive for the reasons set forth in final Office Action that Applicants' claims are not drawn to alleged synergism. To this response, the evidence of synergism provided in the declaration is not commensurate in scope with the breadth of the claims sought to be patented. Claims must be commensurate in scope (synergism) and this is deemed proper since both the combination and its utility is well-known to treat respiratory disorder as taught by Carling et al. and formoterol is effective alone for the treatment of COPD (respiratory disorder). Therefore the treatement of COPD utilizing Carling et al's combination is obvious.

Applicants' rebuttal argument that in the present case, the prior art did not teach that COPD could be treated successfully with budesonide individually therefore the three cases cited by the Examiner is not controlling. This is not persuasive because it is clear by (U) reference that formoterol is effective for the treatment of COPD and it is clear that COPD patients has been

treated by budesonide as taught by (V) reference. The (V) reference teaches the risk involved with relatively high dose of corticosteroid use in chronic treatment of COPD, this does not teach away that budesonide is still effective for the treatment of COPD. Moreover, the combination is well taught by Carling et al. for the treatment of respiratory disorders (COPD). It would have been obvious to one of ordinary skill in the art to treat COPD with the combination taught by Carling et al. with low dose range of budesonide for the short-term duration since Carling et al. teaches various range of dosages of budesonide can be employed. (page 6, lines 25-28). There is expectation of success because Carling reference teaches the combination in various ranges of dosages (low to high) being useful for the treatment of respiratory disorders and both active agents are known to have effectiveness and used for the treatment of COPD as indicated above.

Applicants' rebuttal argument that while reference V discloses that COPD patients receive budesonide treatment, the reference does not report any positive effect on any COPD phenotype thus the Examiner's further request for evidence of a synergistic effect was unfounded. This is not persuasive because (U) reference teaches that formoterol is effective alone for the treatment of COPD and (V) reference teaches that budesonide may be used to treat COPD if first tested on the patient and have efficacy. Therefore with the proviso that drug is tested on the patient first individually and effective then you can use it for the long periods of the time is the suggestion that this medication can be use for the treatment of COPD in individual bases for the long term. Moreover, the combination is well-known by Carling et al. for the treatment of respiratory disorder (COPD). There fore the request for evidence of a synergistic effect was deemed proper.

Applicants' rebuttal argument that the results must be commensurate in scope with the claims was misplaced since the declaration of Jan Trofast, submitted April 25, 2002 is sufficient evidence of unexpected results to overcome the Examiner's rejection in view of the cited art and the declaration of Dr. Hultquist on December 13, 2002, to evidence to overcome the rejection. This is not persuasive because in light of the cited art by the Examiner that the combination of active agents (budesonide and formoterol) are well-known by Carling et al. for the treatment of respiratory disorder not only asthma but other respiratory disorders (e.g. COPD). This indicates that the above combination is useful and effective for the treatment of other respiratory disorders (e.g. COPD as well-known respiratory disorder as disclosed by Saunder's Manual of Medical Practice) other than asthma. Each of active agents is effective and has some benefit in treating COPD individually as taught by (U) and (V) references and also indicated in the Trofast Declaration. Therefore, it would have been obvious to one of ordinary skill in the art to utilize Carlings' combination effective for the treatment of respiratory disorder (e.g. COPD) to conveniently treat a patient suffering from COPD with mono formulation taught by Carling. There is a reasonable expectation of successfully treating COPD because the combination is well-known by Carling for the treatment of other respiratory disorders (e.g.COPD). Moreover, formoterol is well known and effective for the treatment of COPD and budesonide are used for the treatment of COPD patients.

Applicants' finally argue that the Examiner's rejection must be based on the knowledge of one having ordinary skill in the art at the time the application was filed and the request of proof of a synergistic effect based on Applicant's own teachings, including the teachings of the Trofast declaration and not on the teachings of the prior art and the time the application was

filed, it was not understood that the two compounds would have any therapeutic effect on COPD when administered individually or in combination. Again, this is not persuasive because the combination is known to treat respiratory disorders other than asthma and respiratory disorders includes COPD and it is well-known by Saunder's Manual of Medical Practice. The active agent, formoterol is well-known by (U) reference for the treatment of COPD. The active agent, budesonide is used to treat COPD. Therefore, one of ordinary skill in the art would be motivated to treat respiratory disorders (e.g. COPD) utilizing Carling's combination well-known for the treatment of respiratory disorders and contains formoterol particularly effective for the treatment of COPD and also contain budesonide routinely used for the treatment of COPD, for the convenience of having two agents utilized in same respiratory disorder i.e. COPD.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Supervisory Examiner
Art Unit 1617

12/23/03

jmk
December 22, 2003

Conferees

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